Anticoagulants for the Prevention and Treatment of Venous Thromboembolism in Humans Exposed to Microgravity: A Hybrid Systematic and Narrative Review

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Key points:

- Microgravity causes venous stasis, endothelial dysfunction, and hypercoagulability, elevating VTE risk during long-duration spaceflight.
- Only one in-flight internal jugular thrombosis has been documented; evidence on anticoagulation efficacy in space is limited.
- Our systematic review of 13 biomedical and space-agency databases found zero studies meeting PICOS criteria on anticoagulant use in microgravity.
- Diagnostic hurdles include limited ultrasound capability and impractical D-dimer assays; real-time biomarkers and automated imaging are priorities.
- Candidate countermeasures: structured exercise, compression therapy, low-dose direct oral anticoagulants, and machine-learning risk scores integrating mission and physiologic data.
- Potential need for pharmacokinetic studies and operational anticoagulation trials to safeguard astronaut health on future long-duration missions.

ABSTRACT

Importance: Microgravity induces physiological changes that may predispose astronauts to venous thromboembolism (VTE), yet no studies have directly evaluated the safety or efficacy of anticoagulation in this environment.

Objective: To perform a systematic review of anticoagulant use for VTE prevention and treatment in microgravity-exposed individuals and, in the absence of eligible studies, to synthesize existing physiologic and terrestrial evidence relevant to VTE risk and thromboprophylaxis.

Methods: A comprehensive search of 13 biomedical and aerospace databases (MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, CINAHL, NASA Technical Reports Server, ESA archives, ClinicalTrials.gov, NASA Life Sciences Data Archive, ISS Publications Archive, DLR database, NASA SS Research Database) was performed following PRISMA guidelines. Eligible studies included astronauts or individuals in microgravity analogs receiving pharmacologic anticoagulation for VTE prevention or treatment.

Results: The search yielded zero studies meeting predefined PICOS criteria. To contextualize this absence of evidence, we synthesized key physiologic findings from microgravity and ground-based analog studies demonstrating venous stasis, endothelial dysfunction, increased fibrinogen synthesis, altered platelet function, and hypercoagulability.

Conclusions and Relevance: VTE appears rare in spaceflight, but the absence of direct evidence on anticoagulation underscores a critical research gap. Further studies are needed to evaluate anticoagulant safety and efficacy in microgravity, adapt risk assessment tools, and develop evidence-based protocols to safeguard astronaut health.

INTRODUCTION

As humanity prepares for long-duration space exploration, understanding health risks in microgravity has become a critical priority. One such emerging concern is venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Although VTE is well-characterized on Earth, its behavior in the spaceflight environment remains poorly defined. Microgravity induces profound physiologic alterations: cephalad fluid shifts, venous distension, reduced shear stress, endothelial dysfunction, and changes in coagulation pathways that may create conditions favorable to thrombosis [1-4]. Concerns intensified following the first documented case of internal jugular vein (IJV) thrombosis during an International Space Station (ISS) mission in 2019, an event discovered incidentally during ultrasound imaging for fluid-shift research rather than clinical symptoms [5].

Despite this event and growing evidence that microgravity produces venous stasis and coagulation perturbations, clinical data remain extremely limited. No studies to date have examined the safety or efficacy of anticoagulants for VTE prevention or treatment in astronauts or individuals exposed to microgravity analogs. Given the operational challenges of diagnosing and managing VTE in space, understanding whether terrestrial anticoagulation strategies translate safely to spaceflight holds important implications for astronaut health and mission readiness.

To address this gap, we conducted a systematic review across 13 biomedical and aerospace databases following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. As no studies met inclusion criteria, we restructured this work as a hybrid systematic and narrative review: we report the results of the empty systematic search, and we synthesize physiologic and terrestrial evidence relevant to thrombosis risk and potential prophylactic strategies. This hybrid approach acknowledges the scientific value of empty systematic reviews, formally documenting evidence gaps, while contextualizing current understanding of microgravity-induced changes in venous physiology, coagulation, and potential implications for anticoagulation use in space.

As future missions extend beyond low Earth orbit, potentially involving older, medically diverse commercial participants, defining evidence-based risk mitigation strategies for VTE becomes increasingly urgent. This review aims to clarify the current knowledge landscape, identify gaps, and outline priorities for future research to ensure safe and effective management of thrombotic risk during prolonged spaceflight.

METHODS

This review was conducted as a hybrid systematic and narrative synthesis following the PRISMA 2020 guidelines. The objective was to identify studies evaluating the efficacy or safety of pharmacological anticoagulation for the prevention or treatment of VTE in individuals exposed to microgravity. Given that the systematic search yielded no eligible studies, we integrated a structured narrative synthesis of physiologic evidence relevant to VTE risk in microgravity.

Search strategy

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed to identify studies evaluating the efficacy and safety of pharmacological anticoagulation for the prevention and treatment of VTE in microgravity. The search covered MEDLINE (via PubMed), Embase, Scopus, Web of Science, Cochrane Library, CINAHL, NASA Technical

Reports Server (NTRS), European Space Agency (ESA) archives, ClinicalTrials.gov, NASA Life Sciences Data Archive, ESA Erasmus Experiment Archive, ISS Publications Archive, German Aerospace Center (DLR) database, and NASA Space Station Research Database. The final search was conducted on February 3, 2025. The search strategy incorporated Medical Subject Headings (MeSH) terms and keywords related to VTE, anticoagulation, DVT, PE, spaceflight, microgravity, and astronaut health. Boolean operators (AND/OR) were applied to refine results. No date or language restrictions were applied to maximize retrieval.

Eligibility criteria and study selection

Predefined PICOS criteria (Table 1) guided study selection. Studies were eligible if they involved astronauts or individuals in spaceflight-like conditions, examined pharmacological anticoagulation strategies, and reported VTE prevention, treatment efficacy, or associated complications. Studies focusing solely on hypobaric environments were excluded, as they present distinct physiological challenges. All study designs were considered. The literature search was conducted by two independent researchers, with title, abstract, and full-text screening performed independently by one researcher and verified by the second. No formal quality assessment was performed, as no eligible studies were identified. Due to the absence of studies, no data synthesis was conducted. The search and selection process is illustrated in the PRISMA flow diagram (Figure 1), and a PRISMA checklist was completed for relevant systematic review items.

Handling of empty systematic review findings

In accordance with Cochrane guidance on empty reviews, the absence of eligible studies was explicitly documented and presented in the Results. To provide meaningful interpretation, the review incorporated a high-level synthesis of venous and coagulation physiology in microgravity.

RESULTS

Systematic search results

A total of 76 studies were initially retrieved from the search, of which 8 duplicates were removed. The remaining 68 studies were screened for eligibility. Of these, 5 studies proceeded to full-text review, but none met the inclusion criteria. These studies were excluded primarily because they focused on terrestrial thrombosis, fluid shifts without direct VTE outcomes, or theoretical discussions on astronaut health. A detailed list of the excluded studies and their reasons for exclusion is presented in Table 2.

Had eligible studies been identified, a qualitative or quantitative synthesis would have been conducted to assess the efficacy of anticoagulation strategies in microgravity. The absence of relevant studies highlights a substantial gap in the literature, underscoring the urgent need for targeted research in this field.

The effect of microgravity on coagulation and venous function

Microgravity has significant effects on the coagulation cascade, which are particularly relevant in the context of managing VTE in space. The unique environment of microgravity induces several physiological changes that can enhance the coagulation state and increase the risk of VTE.

Firstly, microgravity leads to a headward fluid shift, resulting in venous stasis, particularly in the cephalad venous system. This stasis is characterized by increased IJV distension, elevated venous pressures, and decreased or even reversed blood flow, which are critical factors in thrombus formation [1, 3]. On Earth, the resistance gradient within the vascular system counterbalances the gravitational pressure gradient, ensuring proper blood distribution throughout the body. In the absence of gravity in space, this resistance gradient is unopposed, leading to a preferential redistribution of blood toward the head (Figure 2) [4].

Secondly, microgravity affects endothelial function and the coagulation cascade. Studies have demonstrated increased levels of fibrinogen and thrombin generation markers, signaling a hypercoagulable state. Endothelial damage, likely driven by altered shear stress and venous distension, further exacerbates this prothrombotic environment [3, 6].

Additionally, platelet function is altered in microgravity. Platelet aggregation and adhesion are inhibited, which paradoxically may contribute to a prothrombotic state by impairing normal hemostatic responses and promoting abnormal clot formation under certain conditions [7, 8].

In summary, microgravity enhances the coagulation cascade through venous stasis, endothelial dysfunction, and altered platelet function, all of which contribute to an increased risk of VTE during spaceflight (Virchow's Triad).

Evidence from studies

A systematic review by Kim, D.S., et al. (2021 [3]) critically evaluated the available literature on venous physiology and coagulation in ground-based analogues and actual microgravity environments offering an overview of key findings related to blood flow disturbances, endothelial dysfunction, and hypercoagulability.

Ground-based analogue effects on the venous system

Across six studies using ground-based analogues, several changes in venous flow and distension parameters indicated increased venous stasis and wall stress (Table 3). Two dry immersion (DI) studies reported decreased blood velocity, with one (Moreva, 2008 [9]) documenting reduced basal venous flow rates in both the head and lower extremities after seven days of DI in eight participants. Blood velocity declined across all vessel types, with a greater reduction in veins. Similarly, Navasiolava et al. (2010 [10]) observed decreased calf vein flow rates, elevated endothelial microparticles, and endothelial dysfunction by day three of a seven-day DI study, suggesting impaired venous flow and endothelial function.

Head-down tilt (HDT) studies also demonstrated venous distension and reduced flow. Marshall-Goebel et al. (2016 [1]) found increased IJV cross-sectional area and decreased cerebral outflow during −12° HDT. Long-term head-down bed rest (HDBR) studies further supported these findings. Arbeille et al. (2001 [11]) reported a 40% increase in jugular vein cross-sectional area and a 35% decrease in femoral vein area after 42 days of −6° HDBR. Bleeker et al. (2004 [12]) observed increased leg venous flow resistance and reduced venous compliance after 18 days of −6° HDBR. More recently, Ogoh et al. (2020 [13]) reported reduced jugular vein flow and differential cerebral blood flow patterns, with posterior circulation preserved but significant reductions in anterior circulation during 30 days of −6° HDBR. Collectively, these studies highlight the venous flow disturbances and endothelial changes associated with microgravity analogues.

Microgravity effects on the venous system

Five studies evaluated the effects of microgravity on venous physiology, including one conducted during parabolic flight and four in actual spaceflight (Table 3). Overall, these studies reported increased jugular venous pressure, enlarged cross-sectional areas, and evidence of decreased or reversed venous flow in the upper body.

In parabolic flight, Martin et al. (2016 [14]) observed elevated internal jugular venous pressures using compression sonography, with values rising from 9.9 ± 5.1 to 23.9 ± 5.6 mmHg, consistent with venous distension and wall stress. Similar increases in jugular venous pressure were also noted during simulated lunar (1/6 g) and Martian (1/3 g) gravity conditions compared to normal gravity.

Spaceflight studies consistently demonstrated venous changes. Herault et al. (2000 [15]) reported increased jugular (23–30%) and femoral (33–70%) vein cross-sectional areas during long-duration missions aboard the MIR space station. Arbeille et al. (2015 [16]) observed similar trends in 10 ISS astronauts, with jugular vein cross-sectional area increasing by 178% at 15 days and 225% at 5 months, alongside increases in portal vein size and decreased calf vein cross-sectional area during flight. Fortrat et al. (2017 [17]) documented a rise in lower limb venous compliance and a significant reduction in venous emptying during spaceflight, both of which normalized post-flight in 24 ISS cosmonauts.

In the most recent study, Marshall-Goebel et al. (2019 [1]) evaluated 11 ISS crew members and found a 70.3 mm^2 increase in jugular vein cross-sectional area and a rise in venous pressure from 5.1 to 21.1 mmHg by flight day 150. Critically, stagnant or reversed jugular venous flow was observed in over half (55%) of the participants, and one crew member developed an occlusive thrombus in the internal jugular vein. A retrospective review suggested another participant may have experienced a partial thrombus, marking the first direct observation of thrombus formation in space.

Ground-based analogue effects on the coagulation system

Two studies investigated coagulation during HDBR using thromboelastometry (TEM), thrombin generation, or standard laboratory markers, involving only male participants screened for genetic or medical conditions prior to enrollment (Table 3).

Cvirn et al. (2015 [18]) evaluated 11 participants undergoing 21-day HDBR and reported increased clotting times and decreased alpha angles compared to baseline. Thrombin generation analysis showed reduced peak thrombin and velocity index at day 2, which normalized over the following days. Upon re-ambulation, participants exhibited shortened lag time, decreased time-to-peak, and increased thrombin generation parameters, including peak thrombin and velocity index. Additionally, elevated levels of thrombin–antithrombin complexes and prothrombin fragments were observed during re-ambulation, suggesting enhanced in vivo thrombin generation alongside increased in vitro thrombin-generating capacity.

Haider et al. (2013 [19]) studied 24 participants over 60 days of HDBR, comparing groups with and without exercise. While no significant changes in TEM values were noted between groups, the control group (no exercise, n = 9) displayed significant shortening of clot time, increased alpha angle, and increased fibrinogen-based maximum clot firmness during HDBR, which became even more pronounced during re-ambulation. D-dimer levels and markers of thrombin generation, such as thrombin–antithrombin III complexes and prothrombin fragment F1+2, also progressively increased throughout the study.

Microgravity effects on the coagulation system

Three studies examined the effects of microgravity on coagulation parameters, though none provided data from in-flight measurements (Table 3).

Stein and Schluter (2006 [20]) assessed plasma protein synthesis rates in five astronauts before and after a 16-day Space Shuttle mission. They observed a significant post-flight increase in the fractional protein synthesis rate of fibrinogen (29.6 ± 4.7%) compared to pre-flight levels (19.6 ± 3.5%). Similarly, Kuzichkin et al. (2010 [21]) studied five cosmonauts following short-duration spaceflight (10–11 days) and reported a significant increase in fibrinogen levels. They also noted a non-significant trend toward shorter thrombin time, activated partial thromboplastin time, and reduced antithrombin levels, suggesting a hypercoagulable state. However, no significant changes were found in D-dimer, international normalized ratio (INR), or plasminogen activity. Larina et al. (2017 [22]) conducted proteomic blood analyses on 18 cosmonauts at three time points: 30 days pre-flight, on the day of return, and 7 days post-return from long-duration ISS missions. They identified a significant increase in fibrinogen alpha-chain levels both on the day of return (7651 ± 1350 fmol/μl) and 7 days later (7727 ± 1492 fmol/μl) compared to pre-flight levels (6782 ± 2899 fmol/μl). However, no significant changes were detected in factors VII, IX, X, XI, XII, other fibrinogen chains, prothrombin, or plasminogen.

Assessing risk of VTE in space

Risk factors unique to space

Immobility and decreased physical activity during long-duration missions exacerbate the risk of VTE in space. The limited mobility often experienced by astronauts leads to prolonged venous stasis, further promoting the conditions necessary for clot formation [10].

Another important well established risk factor is space radiation. Studies have shown that space radiation poses a great challenge on cardiac outcomes. The exact mechanism is multifactorial and includes endothelial damage and vascular remodeling, which can compromise vascular integrity and promote clot formation [23].

Developing a space-specific risk assessment algorithm

To assess the risk of VTE in space, a space-specific risk assessment algorithm must account for the unique physiological changes induced by microgravity (Figure 3). One crucial factor is the duration of microgravity exposure. Longer missions, such as those to Mars, carry an increased risk due to prolonged exposure to the physiological changes associated with microgravity. The algorithm must consider mission duration to predict the cumulative risk of VTE, as extended exposure to microgravity leads to the accumulation of these changes over time [6].

Physical fitness and pre-mission conditioning also play a significant role. Astronauts with higher levels of cardiovascular fitness may experience less venous stasis, as their circulatory systems are better adapted to cope with the altered fluid dynamics of microgravity. Moreover, physical activity levels during the mission should be factored into the risk calculation, as increased movement can help mitigate the risks associated with immobility and venous stasis [10]. Current in-flight exercise countermeasures include the Advanced Resistive Exercise Device (ARED) for strength training, treadmill running with a harness that simulates 80% of body weight to mimic gravitational loading, and stationary cycling. These measures specifically aim to counteract the effects of venous stasis, one of the three components of Virchow's triad. However, it is important to note that despite these protocols, up to 17% of astronauts may still experience measurable deconditioning, suggesting that exercise alone may not fully prevent the hemodynamic changes associated with microgravity [24].

Age, smoking history, and pre-existing medical conditions, such as a history of DVT, PE, or cardiovascular disease, must also be incorporated into the algorithm [25]. Finally, medications taken before or during the mission, including hormonal agents or drugs that influence coagulation, should be carefully considered in the overall risk calculation [26].

Current NASA protocols emphasize these principles through preflight screening and in-flight countermeasures. According to the updated NASA 2025 Spaceflight Medical Operations Manual [27], all astronaut candidates undergo thrombophilia screening during their first annual medical exam. This includes testing for cardiolipin antibodies, activated protein C resistance, prothrombin gene mutation, protein C and S deficiency, antithrombin deficiency, antiphospholipid antibodies, and Factor V Leiden. The presence of a family history of unprovoked VTE is also considered a risk factor. In female astronauts using estrogen-containing contraceptives, conversion to progestin-only formulations is recommended. In-flight, pharmacologic agents such as low-molecular-weight heparin (LMWH), apixaban, and aspirin may be available onboard and administered under the direction of a flight surgeon when clinically indicated. Color Doppler ultrasound is also available on the ISS for diagnostic evaluation [28]. These measures likely contribute to the remarkably low reported incidence of VTE in space to date. However, as commercial and long-duration missions evolve, risk profiles may diversify. A space-specific risk algorithm must therefore complement, not replace, current NASA protocols especially given that future crews may include individuals with greater age variation or underlying comorbidities.

Diagnosing VTE in space

Use of biomarkers for diagnosing VTE

Thrombosis diagnosis in space does not currently rely on biomarkers such as D-dimer, and their diagnostic value for VTE in microgravity remains unclear. Microgravity also introduces practical challenges for obtaining and processing blood samples, requiring specialized equipment and adapted collection methods to ensure adequate sample quality [6, 29]. Several emerging technologies, such as portable point-of-care platforms capable of measuring coagulation markers including D-dimer and thrombin generation, have demonstrated technical feasibility, though they remain experimental and unvalidated for use in spaceflight [30, 31]. Wearable biosensors and other miniaturized systems are being explored for continuous physiologic monitoring [29, 32, 33], but their role in VTE detection or risk assessment has not yet been established. Importantly, these biomarkers have not been validated for diagnostic use in IJV thrombosis on Earth, and their applicability to spaceflight remains unproven.

Ultrasound and non-invasive diagnostic techniques

Ultrasound, a widely used diagnostic tool for detecting DVT on Earth, faces unique challenges in space. In microgravity, traditional positioning required for ultrasound imaging is difficult, as stabilizing both the patient and the probe becomes problematic. Additionally, microgravity-induced air bubbles in the blood can interfere with image quality [34, 35]. To address these challenges, space agencies are developing portable, handheld ultrasound devices specifically designed for zero-gravity environments. These systems should enable easy operation and ideally include automated image interpretation to aid in the rapid and accurate diagnosis of VTE [34-36]. Remote echography is another innovative approach, utilizing tele-operated systems with motorized probes, which allow ground-based sonographers to control the examination remotely. This method has been successfully used on the ISS to image the carotid artery, jugular vein, and other organs [34]. Advancements in 3D ultrasound technology provide consistent and accurate measurements of the IJV, mitigating angulation errors and improving assessments of venous congestion in space [35]. Furthermore, the integration of deep learning algorithms for automated image interpretation enhances diagnostic accuracy, enabling astronauts to self-assess DVT risk with minimal training [36, 37].

Treating VTE in space

If VTE is diagnosed during space travel, any prophylactic anticoagulation dose would need to be adjusted to a therapeutic dose to effectively treat the acute thrombotic event. According to the ACCP guidelines, DOACs such as apixaban and rivaroxaban are preferred over vitamin VKAs for the treatment of active VTE due to their favorable efficacy and safety profiles [38, 39]. The recommended initial treatment regimens for DOACs involve higher doses during the early phase of therapy. For apixaban, the standard dosage is 10 mg twice daily for the first 7 days, followed by 5 mg twice daily. For rivaroxaban, the initial dosage is 15 mg twice daily for the first 21 days, followed by 20 mg once daily [39].

The unique challenges of spaceflight, such as limited medical resources and constraints on routine monitoring, make DOACs particularly suitable for this setting. Their fixed dosing, lack of need for regular laboratory monitoring, and lower risk of intracranial bleeding compared to VKAs provide distinct advantages [39, 40]. However, further investigation into their behavior in microgravity is essential to ensure that dosing remains both safe and effective [41-43]. Among DOACs, apixaban may be especially favorable in space due to its slightly lower bleeding risk compared to rivaroxaban, offering an additional safety margin in this unique environment [39].

LMWH such as enoxaparin, also holds significant promise for space missions. Its subcutaneous administration and established safety profile make it an attractive option, particularly as it does not require frequent monitoring. However, the mechanics of administering injections in microgravity and the potential effects on absorption and distribution need to be addressed [44, 45].

In contrast, warfarin, despite its historical prevalence as an anticoagulant, is less suitable for use in space. Its need for frequent INR monitoring, susceptibility to numerous drug and dietary interactions, and potential variability in response under microgravity conditions make it a challenging choice for extended missions [46, 47].

Preventing VTE in space

The prevention of VTE in space is a critical concern due to the unique physiological changes induced by microgravity. These changes include altered venous hemodynamics, increased fibrinogen and coagulation markers, hypoalbuminemia, and immune dysfunction, which collectively contribute to an increased risk of VTE [1, 6, 25]. Several key preventive strategies have been identified to address this risk.

Microgravity and anticoagulant pharmacokinetics

The primary prevention and treatment for VTE involves anticoagulation therapy, but selecting suitable anticoagulants for space requires a thorough understanding of their pharmacological properties and the effects of microgravity on drug behavior. Microgravity introduces significant changes to the absorption, distribution, metabolism, and elimination of medications, all of which are critical for maintaining therapeutic efficacy during space missions.

Microgravity can affect the absorption of orally administered anticoagulants, such as apixaban and rivaroxaban, by altering gastrointestinal motility. These changes may impact the rate and extent of drug absorption, potentially necessitating dose adjustments to maintain therapeutic plasma levels [42, 43]. Additionally, the redistribution of body fluids and reduction in plasma volume in microgravity can influence drug distribution, leading to changes in drug concentrations that might require tailored dosing strategies [41, 44].

Metabolism and elimination of anticoagulants may also be altered in space due to microgravity-induced changes in liver function and enzyme activity. Variations in the activity of key drug-metabolizing enzymes and transporters, such as P-glycoprotein, could further complicate the pharmacokinetics of anticoagulants [32, 42, 48]. These physiological changes highlight the need for research into how microgravity affects the pharmacodynamics of commonly used anticoagulants.

Pharmacological prophylaxis

Pharmacological prophylaxis, including anticoagulants, may be considered for astronauts at high risk of VTE, especially those with additional risk factors such as the use of oral contraceptives; however, the risk of bleeding in the space environment must be carefully balanced [26].

Evidence supporting the use of oral anticoagulants for VTE prevention

Table 4 summarizes the evidence supporting the use of oral anticoagulants for use in preventing DVT in patients post-unprovoked DVT, post-surgery, and those with malignancy. Importantly, VTE incidence rates in these terrestrial populations are substantially higher than those observed during spaceflight, where only one confirmed case of internal jugular vein thrombosis has been reported to date, with one additional suspected but unconfirmed case and no other definitive VTE events described. While these populations are distinct from astronauts, the underlying rationale for anticoagulation, preventing recurrent thrombosis in individuals at elevated risk, can be cautiously extrapolated to long-duration space missions, where astronauts may experience a prothrombotic state due to microgravity-induced vascular changes.

Post-unprovoked DVT

For individuals with a first unprovoked DVT, multiple meta-analyses show that extended oral anticoagulant therapy significantly lowers the rate of recurrent VTE compared with discontinuation [49, 50]. Both the American College of Chest Physicians (ACCP) and the American Society of Hematology (ASH) recommend extended anticoagulant therapy for patients with a first unprovoked proximal DVT, particularly for those with a low or moderate bleeding risk [51, 52].

Post-surgery

Direct oral anticoagulants (DOACs) are widely recommended for thromboprophylaxis following major orthopedic procedures, such as total hip or knee arthroplasty. Evidence from systematic reviews and guidelines indicates that agents like apixaban, rivaroxaban, and dabigatran reduce symptomatic VTE and show bleeding rates comparable to standard approaches [51, 53-55]. These findings underscore the effectiveness of DOACs in settings where transient but clinically meaningful postoperative risk exists.

Malignancy

In cancer-associated thrombosis, long-term anticoagulation with oral agents including apixaban, rivaroxaban, and edoxaban has been supported by multiple randomized trials. These studies show reduced recurrence compared with older therapies, with careful consideration of bleeding risk depending on tumor location [56-59]. The National Comprehensive Cancer Network (NCCN) guidelines similarly recommend DOACs for most patients with cancer-associated VTE when bleeding risk is acceptable [60].

Risk of bleeding in space

The risk of spontaneous bleeding in space, particularly in the context of low-dose anticoagulation, appears to be minimal based on current evidence. However, this assessment is limited by the extremely low number of documented VTE events in astronauts and the relatively small size of the astronaut population. As a result, there is very limited in-flight experience with anticoagulant use, which restricts our ability to draw firm conclusions about bleeding risk in this setting. A systematic review by Kim et al. (2021 [3]) highlights that while microgravity may promote a hypercoagulable state due to changes in venous flow, distension, pressures, and endothelial damage, there is no substantial evidence to suggest an increased risk of spontaneous bleeding in healthy individuals during spaceflight. Similarly, White and Wenthe (2023 [32]) discuss hemostasis management in space and report that although space travel influences vascular biology and coagulation, these physiological changes do not inherently raise the likelihood of spontaneous bleeding. In conclusion, the likelihood of spontaneous bleeding in healthy individuals using low-dose anticoagulation in space is extremely low.

Non-pharmacological prophylaxis

Alongside anticoagulation therapy, non-pharmacological treatments play a crucial role in the prevention and management of VTE by reducing the reliance on medications and addressing unique risks associated with spaceflight. Exercise therapy is essential in promoting circulation and preventing venous stasis. Regimens designed to maintain cardiovascular fitness in space, such as resistance training, aerobic exercise, and mobility exercises, may help reduce thrombosis risk. Countermeasures like artificial gravity and lower body negative pressure have shown promise in preserving cardiovascular and musculoskeletal function during extended space missions [10, 61, 62]. In contrast to terrestrial settings, spaceflight is characterized by cephalad fluid shifts rather than dependent lower-limb venous pooling, which limits the theoretical applicability of compression-based strategies such as compression stockings or intermittent pneumatic compression. While these modalities are well established for VTE prevention on Earth [63, 64], there is currently no evidence supporting their effectiveness in the microgravity environment.

DISCUSSION

This hybrid systematic and narrative review highlights the absence of studies directly evaluating anticoagulation strategies for VTE prevention or treatment in astronauts or microgravity analogs. Despite an extensive search, no publication met PICOS criteria, demonstrating how limited current evidence remains in this domain. As a result, understanding of VTE in spaceflight continues to depend on terrestrial data and physiologic observations from space missions and analog environments. These sources provide useful context but cannot fully replace targeted research conducted under microgravity conditions.

Astronauts represent a unique population with specific health risks, but it is essential to acknowledge the changing landscape of space exploration. Historically, space agencies have selected highly trained, medically screened individuals with exceptional physical fitness. However, with the rise of commercial spaceflight, astronauts may no longer be exclusively elite individuals but could include a more diverse cohort with varying medical histories and pre-existing conditions. This shift significantly broadens the relevance of studying thrombosis risk and anticoagulation strategies in a wider group of space travelers, highlighting the need for research that accounts for diverse health profiles.

The remarkably low number of publicly reported VTE cases in spaceflight, estimated at approximately 1 in 600 astronauts [5], suggests that current protocols are highly effective. However, this figure must be interpreted cautiously, as asymptomatic or undiagnosed cases may go unnoticed due to the absence of routine screening for extremity thrombosis. Notably, the documented case involved the IJV, raising questions about whether current preventive strategies, particularly exercise protocols, effectively mitigate risk in the upper venous system. It is also important to consider whether new entrants to commercial spaceflight programs, who may have broader health profiles, will derive similar protection from existing protocols.

Empty systematic reviews, such as this one, play an essential role in the scientific community. By formally documenting the absence of evidence, they highlight potential knowledge gaps, inform policy-making, justify the need for increased funding, and set priorities for future research [65-67]. Our findings, in particular, point to the potential value of experimental models that simulate VTE risk in space-like conditions, studies focusing on the pharmacokinetics of anticoagulants in microgravity, and the development of robust in-mission diagnostic tools and effective therapeutic strategies. Future research should aim to address both the underlying physiological mechanisms and the creation of practical approaches for preventing and managing VTE in space.

CONCLUSION

This review highlights the lack of direct evidence on anticoagulation for VTE in microgravity, with current understanding relying largely on terrestrial studies and physiologic observations. Continued research is needed to clarify thrombotic risk, refine diagnostic strategies, and evaluate therapeutic options suitable for spaceflight. As space exploration ventures further from Earth, and as the realm of commercial and private travel to low Earth orbit burgeons, interdisciplinary collaboration and innovation will be essential to ensure the health and safety of those travelling to space.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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Figure 1 – Search strategy based on PRISMA 2020 flow diagram [68]. Records were identified from databases, then screened and assessed for eligibility.

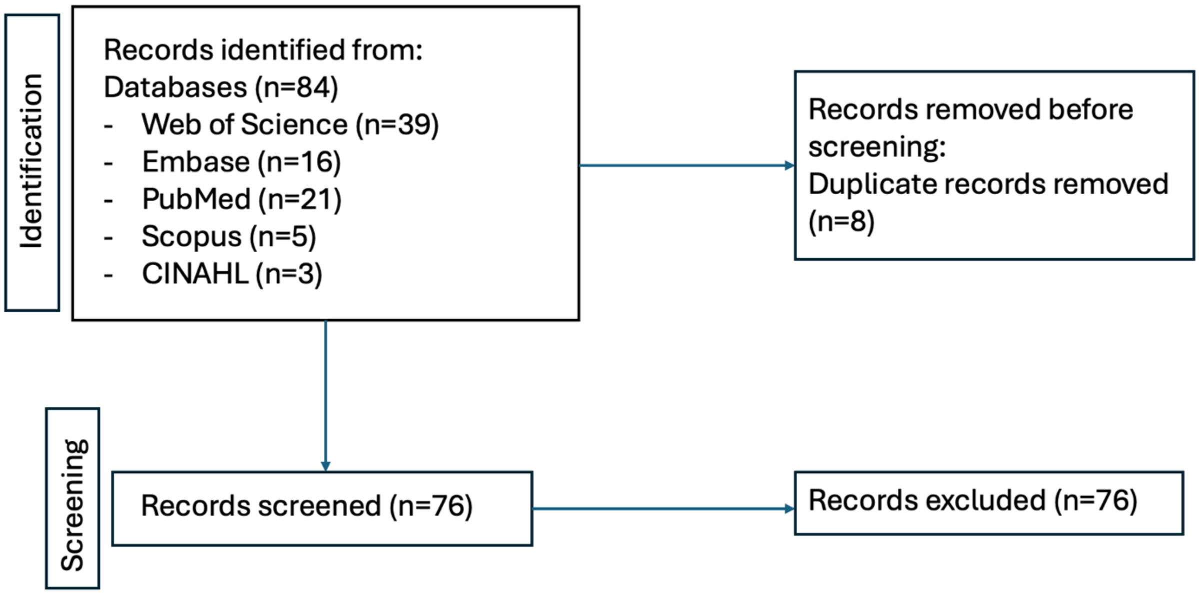

Figure 2 – Comparison of blood distribution on earth and in space

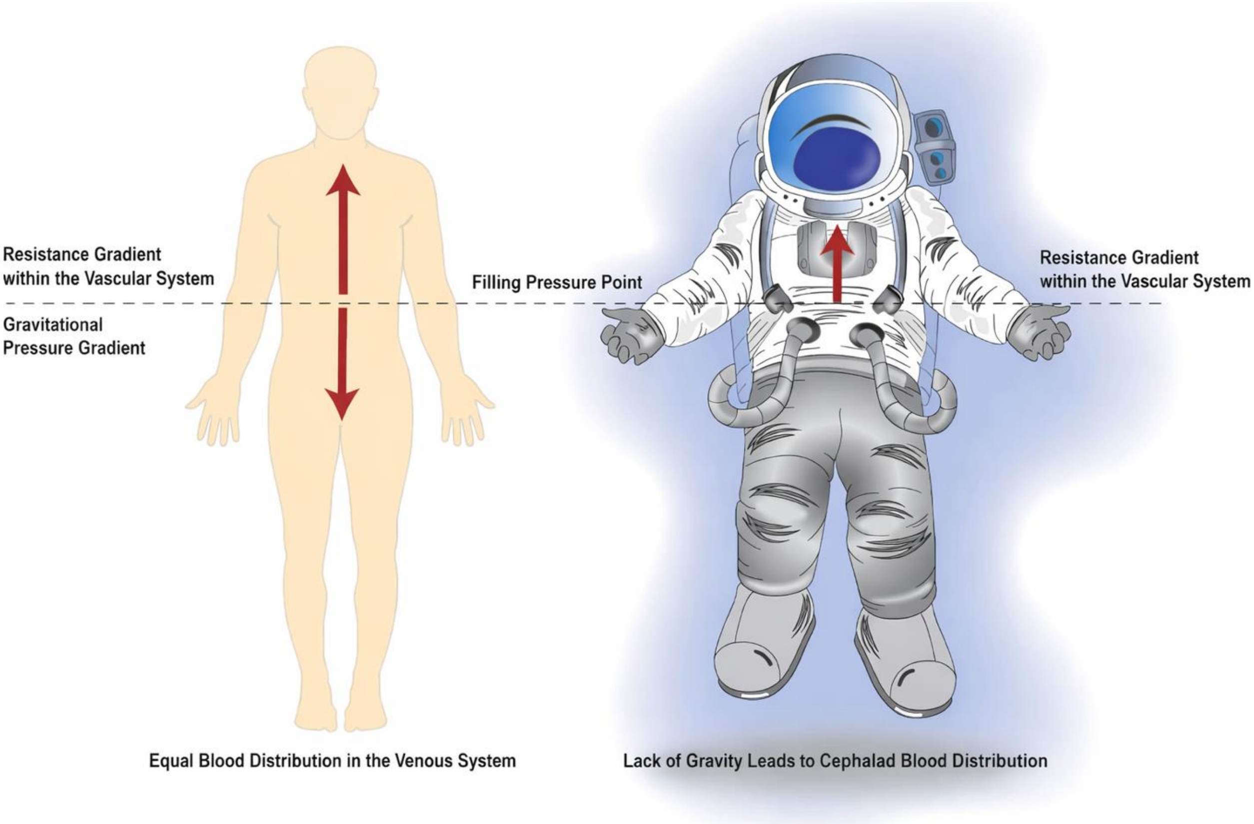

Figure 3 – Space-specific risk assessment for VTE

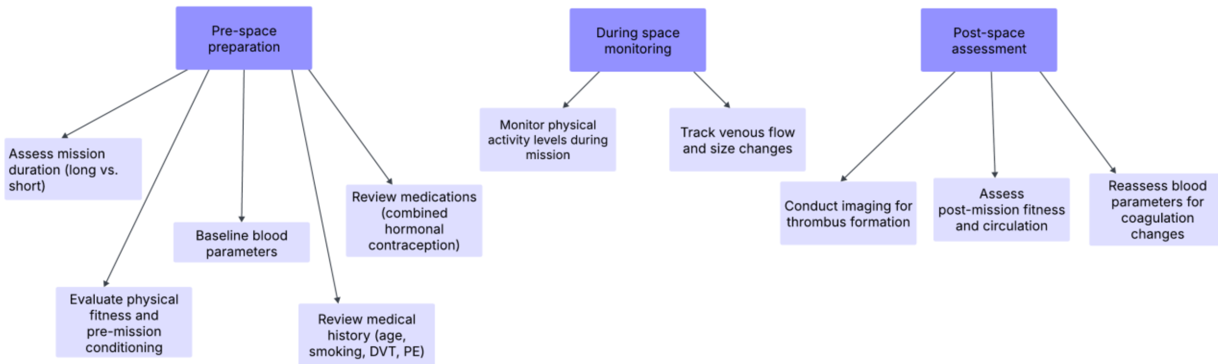

Table 1: PICOS criteria and research question for systematic review on anticoagulant use for VTE in microgravity

PICOS	Description
P (Population)	Astronauts or individuals exposed to microgravity
I (Intervention)	Use of anticoagulants (DOACs, LMWH, warfarin, etc.)
C (Comparison)	No anticoagulation or alternative prophylaxis/treatment
O (Outcomes)	Prevention and treatment efficacy/safety of VTE in microgravity
S (Study Design)	All study designs were considered, with a focus on studies directly addressing VTE outcomes in spaceflight or microgravity conditions

Research question: "What is the efficacy and safety of anticoagulants in preventing or treating venous thromboembolism in microgravity conditions?"

Table 2: Venous and coagulation system changes in microgravity and ground-based analogues

	Effect	Study	Method
Venous changes	Increased JV pressure	Martin et al. (2016)	Parabolic flight (n=11)
		Marshall-Goebel et al. (2019)	Spaceflight (n=11)
	Increased JV CSA	Herault et al. (2000)	Spaceflight (n=6)
		Arbeille et al. (2015)	Spaceflight (n=10)
		Marshall-Goebel et al. (2019)	Spaceflight (n=11)
		Marshall-Goebel et al. (2016)	Head-down tilt at -12° (n=9)
		Arbeille et al. (2001)	-6° head-down bed rest x42 days (n=8)
	Increased FV CSA	Herault et al. (2000)	Spaceflight (n=6)
	Increased portal vein CSA	Arbeille et al. (2015)	Spaceflight (n=10)
	Increased venous compliance	Fortrat et al. (2017)	Spaceflight (n=24)
	Decreased venous emptying	Fortrat et al. (2017)	Spaceflight (n=24)
	Stagnant or reverse flow	Marshall-Goebel et al. (2019)	Spaceflight (n=11)
	Decreased linear blood velocity	Moreva (2008)	Dry immersion x7 days (n=8)
	Decreased basal venous blood velocity	Navasiolava et al. (2010)	Dry immersion x7 days (n=8)
	Increased circulating endothelial microparticles	Navasiolava et al. (2010)	Dry immersion x7 days (n=8)
	Decreased venous outflow	Marshall-Goebel et al. (2016)	Head-down tilt at -12° (n=9)
	Decreased FV CSA	Arbeille et al. (2001)	-6° head-down bed rest x42 days (n=8)
	Increased leg venous flow resistance	Bleeker et al. (2004)	-6° head-down bed rest x18 days (n=11)
	Decreased JV blood flow	Ogoh et al. (2020)	-6° head-down bed rest x60 days (n=10)
Coagulation system changes	Increased fibrinogen synthesis rate	Stein & Schluter (2006)	Spaceflight (n=5)

	Increased fibrinogen	Kuzichkin et al. (2010)	Spaceflight (n=5)
	Increased fibrinogen αchains	Larina et al. (2017)	Spaceflight (n=18)
	Increased TEM CT	Cvirn et al. (2015)	Bedrest x21 days (n=11)
	Decreased TEM alpha angle	Cvirn et al. (2015)	Bedrest x21 days (n=11)
	Increased D-Dimer/TAT/PT F1+F2	Haider et al. (2013)	Bedrest x60 days (n=9)
	Decreased EXTEM CFT	Haider et al. (2013)	Bedrest x60 days (n=9)
	Increased EXTEM alpha angle	Haider et al. (2013)	Bedrest x60 days (n=9)
	Increased FIBTEM MCF	Haider et al. (2013)	Bedrest x60 days (n=9)

All results are statistically significant ($p<0.05$). Abbreviations: CSA, cross-sectional area; FV, femoral vein; JV, jugular vein; CFT, clot formation time; CT, clotting time; EXTEM, extrinsic pathway thromboelastometry; FIBTEM, fibrinogen thromboelastometry; MCF, maximal clot firmness; PT F1+F2, prothrombin fragment F1+2; TAT, thrombin-antithrombin III complex; TEM, thromboelastometry.

Table 3: Evidence supporting the use of oral anticoagulants for preventing VTE in specific patient populations

Patient group	Study	Anticoagulant	Study type	Findings
Post-unprovoked DVT	Khan et al. (2021)	DOACs vs VKAs	Systematic review and meta-analysis	DOACs reduce recurrent VTE compared to VKAs (1.08 vs 1.55 per 100 person-years).
	ACCP guidelines (2016)	DOACs	Clinical practice guidelines	Extended therapy recommended for low/moderate bleeding risk patients with first unprovoked proximal DVT.
	Marik and Cavallazzi (2015)	DOACs vs aspirin	Systematic review and meta-analysis	DOACs more effective than aspirin for reducing recurrent VTE.
Post-surgery	ACCP guidelines (2016)	Apixaban, dabigatran, rivaroxaban	Clinical practice guidelines	DOACs recommended for thromboprophylaxis in THA or TKA due to better efficacy and safety.
	Marcucci et al. (2022)	DOACs	Systematic review and meta-analysis	DOACs significantly reduce symptomatic VTE vs no treatment, with moderate to high certainty; similar bleeding risk to LMWH.
	Haykal et al. (2021)	DOACs vs LMWH	Systematic review and meta-analysis	DOACs reduce major VTE and DVT incidence in orthopedic surgery patients, with no significant difference in major bleeding compared to LMWH.
Malignancy	ASCO guidelines (2020)	LMWH, edoxaban, Rivaroxaban, apixaban	Clinical practice guidelines	Recommendation for long-term anticoagulation with preference for LMWH, edoxaban, rivaroxaban, or apixaban over VKAs. Caution with direct Xa inhibitors in high bleeding risk cancer patients.
	Hokusai-VTE Cancer Trial (2018)	Edoxaban vs dalteparin	Randomized controlled trial	Edoxaban noninferior to dalteparin for preventing recurrent VTE; higher bleeding risk in GI cancer patients.

	SELECT-D Trial (2018)	Rivaroxaban vs dalteparin	Randomized controlled trial	Rivaroxaban reduces recurrent VTE compared to dalteparin; higher clinically relevant non-major bleeding.
	JAMA Clinical Trial (2023)	DOACs vs LMWH	Randomized controlled trial	DOACs noninferior to LMWH for recurrent VTE prevention; similar major bleeding rates.
	NCCN Guidelines (2023)	Apixaban, edoxaban, rivaroxaban	Clinical practice guidelines	Recommendation for DOACs in cancer-associated VTE, especially for patients without gastrointestinal/genitourinary lesions due to bleeding risk.

All results are statistically significant ($p<0.05$). Abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; ACCP, American College of Chest Physicians; THA, total hip arthroplasty; TKA, total knee arthroplasty; LMWH, low molecular weight heparin; GI, gastrointestinal; Xa, factor Xa; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; RCT, randomized controlled trial.

Supplementary Table 1: Summary of studies and reasons for exclusion

Study Title	Authors	Reason for Exclusion
Combination of Traditional Chinese Medicine and Low-Molecular-Weight Heparin Prevents Deep Vein Thrombosis After Surgery: A Meta-Analysis	Chen, C; Tang, Q; Zhang, WJ; Yuan, HJ; Huai, Y; Jiang, K; Wu, YL; Zhao, HP	Not related to microgravity; focuses on surgery-related VTE prevention.
Managing reversal of direct oral anticoagulants in emergency situations Anticoagulation Education Task Force White Paper	Ageno, W; Büller, HR; Falanga, A; Hacke, W; Hendriks, J; Lobban, T; Merino, J; Milojevic, IS; Moya, F; van der Worp, HB; Randall, G; Tsioufis, K; Verhamme, P; Camm, AJ	Not related to microgravity; focuses on reversal of anticoagulants in emergency settings.
Continued commitment to safety: building on the existing rivaroxaban knowledge base	Beyer-Westendorf, J; Haas, S; Turpie, AGG	Not focused on VTE in microgravity or space conditions.
A 65-Year-Old Man with Bilateral Adrenal Hemorrhage Following Prophylaxis for Postoperative Deep Vein Thrombosis with Rivaroxaban	Al-Rawi, S; Seidahmed, M; Emam, SS; Othman, ES	Not related to microgravity; focused on postoperative VTE in non-space conditions.
Prevention and treatment of venous thromboembolism: the place of new oral anticoagulants	Reis, A	Not focused on VTE in microgravity or space conditions.
Optimal management of upper extremity deep vein thrombosis: Is venous thoracic outlet syndrome underrecognized?	Illig, KA; Gober, L	Focuses on upper extremity DVT, not VTE in microgravity.
Recombinant activated factor VII treatment of retroperitoneal hematoma in a patient with renal failure receiving enoxaparin and clopidogrel	Cherfan, A; Arabi, Y; Al Askar, A; Al Shimemeri, A	Not focused on VTE in microgravity or space conditions.
Incidence of upper extremity deep vein thrombosis in the retrosternal reconstruction after esophagectomy	Yamada, L; Saito, M; Suzuki, H; Mochizuki, S; Endo, E; Kase, K; Ito, M; Nakano, H; Yamauchi, N; Matsumoto, T; Kaneta, A; Kanke, Y; Onozawa, H; Hanayama, H; Okayama, H; Fujita, S; Sakamoto, W; Watanabe, Y; Hayase, S;	Not focused on VTE in microgravity or space conditions.

	Saze, Z; Momma, T; Ohki, S; Kono, K	
Pulmonary embolism. Clinical relevance, requirements for diagnostic and therapeutic strategies	Nowak, FG; Halbfass, P; Hoffmann, E	Not related to anticoagulant use in microgravity or space conditions.
Uncommon yet critical: Pulmonary embolism in a 14-year-old Nigerian child: A case report	Amaewhule, OU; Robinson, ED; Iloeje, UN; Nyeche, EO; Emeruwa, VE; Daniel, FM	Not related to microgravity; focuses on pediatric PE case.
Risk of postoperative hemorrhage after intracranial surgery after early nadroparin administration: Results of a prospective study	Gerlach, R; Scheuer, T; Beck, J; Woszczyk, A; Böhm, M; Seifert, V; Raabe, A	Not related to VTE in microgravity; focuses on surgery-related hemorrhage.
Treatment of upper-extremity outflow thrombosis	van den Houten, MML; van Grinsven, R; Pouwels, S; Yo, LSF; van Sambeek, MRHM; Teijink, JAW	Focused on upper extremity thrombosis, not VTE in microgravity.
Successful treatment of superior vena cava syndrome due to internal jugular vein thrombosis in a 55-year-old man with comorbid diabetes mellitus type 2 and pneumonia	Tofan, R; Wardhani, SO; Nurdianto, AR	Not related to VTE in microgravity or space conditions.
Acute ischaemia of the lower limb due to non-bacterial thrombotic endocarditis with recent venous thrombo-embolic disease as the initial manifestation of lung adenocarcinoma: a case report	Polo, J; Raufast, D; Cornand, D; Elias, A	Not related to VTE in microgravity; focuses on endocarditis-related thrombosis.
Cerebral Venous Thrombosis	Zuurbier, SM; Coutinho, JM	Not focused on VTE in microgravity or space environments.
The bedside investigation of pulmonary embolism diagnosis study - A double-blind randomized controlled trial comparing combinations of 3 bedside tests vs ventilation-perfusion scan for the initial investigation of suspected pulmonary embolism	Rodger, MA; Bredeson, CN; Jones, G; Rasuli, P; Raymond, F; Clement, AM; Karovitch, A; Brunette, H; Makropoulos, D; Reardon, M; Stiell, I; Nair, R; Wells, PS	Not focused on VTE prevention or treatment in space environments.

Prevention of fraxiparine venous thromboembolism in patients with a history of extensive orthopedic interventions on the lower limbs.	Neimark, MI; Momot, AP; Zinovyeva, IE	Not related to space-related VTE prevention or treatment.
Axillary vein thrombosis and congenital dysfibrinogenemia in a commercial pilot: A case report	Jagathesan, T; Houston, SJ; Evans, AD	Focuses on non-space-related thrombosis in pilots, not microgravity.
Circulatory collapse, right ventricular dilatation, and alveolar dead space: A triad for the rapid diagnosis of massive pulmonary embolism	Gazmuri, RJ; Patel, DJ; Stevens, R; Smith, S	Not related to anticoagulant efficacy/safety in microgravity.
Diclofenac for reversal of right ventricular dysfunction in acute normotensive pulmonary embolism: A pilot study	Jimenez, D; Nieto, R; Corres, J; Fernández-Golfín, C; Barrios, D; Morillo, R; Quezada, CA; Huisman, M; Yusen, RD; Kline, J	Not related to anticoagulants or microgravity; focuses on PE treatment.
Multifaceted Heparin: Diverse Applications beyond Anticoagulant Therapy	Sultana, R; Kamihira, M	Not focused on VTE prevention or treatment in microgravity.
Development of a postoperative occlusive thrombus at the site of an implanted inferior vena cava filter A case report	Kukida, A; Takasaki, Y; Nakata, M; Nishihara, T; Kitamura, S; Fujii, S; Watanabe, Y; Yorozuya, T	Not related to VTE prevention or treatment in microgravity.
Assessment of thromboprophylaxis in medical patients hospitalized in Andalusia. A multicenter study	Puerto, MAN; Ortega, FJM; Guerrero, RI; Sandubete, EC; Buzón-Barrera, ML; Marín-León, I	Not related to VTE prevention or treatment in microgravity.
Very late unusual thrombosis of the remnant pulmonary vasculatures after lung resection complicated by embolic events	Yoon, HJ; Kim, KH; Jeong, MH; Cho, JG; Park, JC	Not focused on VTE in microgravity or space conditions.
Minor plasma lipids modulate clotting factor activities and may affect thrombosis risk	Deguchi, H; Elias, DJ; Griffin, JH	Not related to VTE in microgravity or space conditions.
Cerebral abscess and thrombophilia in pregnancy - A case report	Baxi, LV; Mayer, SA; Mansukhani, M	Not related to VTE in microgravity; focuses on genetic thrombosis.
Ruptured pulmonary infarction: A rare, fatal complication of thromboembolic disease	Wick, MR; Ritter, JH; Schuller, D	Not focused on VTE prevention or treatment in microgravity.

Possible involvement of cytokines in diffuse intravascular coagulation and thrombosis	Esmon, CT	Not related to VTE in microgravity; focuses on anticoagulation-related bleeding.
Epidural hematoma mimicking transverse myelitis in a patient with primary antiphospholipid syndrome	Kim, WJ; Hong, YK; Yoo, WH	Not related to VTE in microgravity or anticoagulants.
Spontaneous facial hematoma induced by vitamin K antagonist therapy: a rare case report	Mrabet, A; Boulouiz, S; Bilal, M; El Ouafi, N; Bazid, Z	Not focused on VTE prevention or treatment in microgravity.
A Case Series of Life-Threatening Hemorrhagic Events in Patients with COVID-19	Hajian, A	Not related to VTE in microgravity; focused on cases of hematologic disorders in non-space conditions.
THROMBIN ELABORATION IN ENDOTOXIN-INDUCED INTRAVASCULAR FIBRIN DEPOSITION - LEUKOCYTE DEPENDENT PROCESS DISTINCT FROM SYSTEMIC HYPERCOAGULABILITY	LIPINSKI, B; GUREWICH, V; HYDE, E	Not related to VTE prevention in microgravity; focuses on thrombophilia-related complications in pregnancy.
Nonsurgical management of an extensive spontaneous spinal epidural hematoma causing quadriplegia and respiratory distress in a choledocholithiasis patient: A case report	Raasck, K; Khoury, J; Aoude, A; Abduljabbar, F; Jarzem, P	Not related to VTE prevention or treatment in microgravity.
Recurrent thrombosis: a case report of young patient JAK2+ without myeloproliferative disease and other risk factors. The role of sport activity	Sica, A; Sagnelli, C; Sagnelli, E; Fiorelli, A; Casale, B	Not focused on anticoagulants or VTE prevention in microgravity; focuses on blood clotting in non-space settings.
HYPERCOAGULATION SYNDROME: CLASSIFICATION, PATHOGENESIS, DIAGNOSTICS, AND THERAPY	Vorobiev, AI; Vasiliev, SA; Gorodetskiy, VM; Shevelev, AA; Gorgidze, LA; Kremenetskaya, OC; Shklovskiy-Kordi, NE	Not focused on VTE prevention or treatment in microgravity.
MAJOR CLOSE SPACE BLEEDING IN PATIENTS ON ANTICOAGULATION WITH ACENOCUMAROL (TAO) OR NON FRACTIONNED HEPARIN (HS): A CASE-CONTROL STUDY	Lacasa, JM; Juan, N; Juliá, J; Rodríguez-Carballeira, M; de Diego, I; Soto, R; Garau, J	Not related to VTE prevention or treatment in microgravity.

Lipogranulomatous adenopathy: a characteristic but under-recognized presentation of Whipple's disease	Turkington, P; MacDonald, A; Greenstone, M	Not related to VTE prevention or treatment in microgravity.
SPONTANEOUS RETROPERITONEAL HEMORRHAGE	PODE, D; CAINE, M	Not related to VTE in microgravity; focused on anticoagulation-related bleeding.
The Vascular Frontier: Exploring the diagnosis and management of vascular conditions in spaceflight	Drudi L.M., Grenon S.M.	Not focused on evaluating the safety and efficacy of anticoagulants in microgravity (describes a single case, observational findings, and general discussions).
Subarachnoid hemorrhage from sudden gravitational changes	Rabinstein A.A., Braksick S.A., Wijdicks E.F.M.	Not related to VTE prevention or treatment in microgravity.
The authors reply	Auñón-Chancellor, S.M., Pattarini J.M., Moll S.	Does not directly assess the safety or efficacy of anticoagulants in preventing or treating VTE in microgravity (discusses the preference for DOACs for treating VTE in space).
Earthling	Auñón-Chancellor, S	Not focused on the treatment or prevention of VTE in space (reflects personal experiences of an astronaut).
Long-haul flights, edema, and thrombotic events: Prevention with stockings and Pycnogenol supplementation (LONFLIT Registry Study)	Cesarone, M. R.; Belcaro, G.; Geroulakos, G. ; Griffin, M.; Ricci, A.; Brandolini, R.; Pellegrini, L.; Dugall, M.; Ippolito, E.; Candiani, C.; Simeone, E.; Errichi, B. M.; Di Renzo, A.	Not focused on anticoagulant use or VTE in microgravity
Trombofilias and pregnancy-screening and prophylaxis, yes or no?	Plesinac S.	Not focused on anticoagulants in microgravity or VTE prevention/treatment in space

Are patients with preoperative air travel at higher risk for venous thromboembolism following primary total hip and knee arthroplasty?	Citak, Mustafa; Klatte, Till Orla; Suero, Eduardo M. ; Lenhart, Johannes; Gehrke, Thorsten; Kendoff, Daniel	Not focused on anticoagulant use or VTE in microgravity.
Fatal pulmonary embolization after negative serial ultrasounds	Tainter, Christopher R., MD; Huang, Alan W., MD; Strayer, Reuben J., MD	Does not focus on space medicine or spaceflight-related VTE.
Decompression illness	Vann, Richard D, Dr; Butler, Frank K, MD; Mitchell, Simon J, FANZCA ; Moon, Richard E, Prof	Not related to VTE in spaceflight.
Contraception in the cosmos: The combined oral contraceptive pill in space	Murad, Ali	Not directly related VTE in space.
Traveler's thrombosis: International consensus statement	Schobersberger, W; Toff, W D; Eklöf, B ; Fraedrich, G; Gunga, H C; Haas, S; Landgraf, H; Lapostolle, F; Partsch, H; Perschler, F; Schnapka, J; Schobersberger, B; Scurr, J H; Watzke, H	Not specific to spaceflight.
Patent foramen ovale: A new disease?	Drighil, Abdenasser; El Mosalami, Hanane; Elbadaoui, Nadia ; Chraibi, Said; Bennis, Ahmed	Focuses on a cardiac condition, not space-specific thrombosis.
A case of thrombosis: Possible sickle cell?	Akar, Nejat	Not specific to spaceflight.
Unilateral lower limb suspension can cause deep vein thrombosis	Bleeker, Michiel W P; Hopman, Maria T E; Rongen, Gerard A ; Smits, Paul	Experimental model not directly applicable to spaceflight.
Economy class syndrome	Porodko M., Auer J., Eber B.	General air travel-related thrombosis.
Air travel and thrombosis: What about women on HRT	Giangrande, Paul	Not space-specific.
Venous Thrombosis during Spaceflight	Auñón-Chancellor SM, Pattarini JM, Moll S, Sargsyan A.	Case report with no comparative data on anticoagulant efficacy and

		safety in a broader population.
Absent at Birth: An Unusual Case of Deep Vein Thrombosis.	Aday AW, Sobieszczyk PS, Beckman JA.	Case report focusing on an individual with a rare condition, not relevant to spaceflight or VTE in microgravity.
You're the flight surgeon: pulmonary embolism.	Ewing GL.	Does not focus on anticoagulant use for VTE in microgravity or spaceflight-specific conditions.
Prevention of venous thromboembolism: focus on mechanical prophylaxis.	Lippi G, Favaloro EJ, Cervellin G.	Does not involve anticoagulant use for VTE in microgravity or spaceflight-specific conditions. Focuses on mechanical prophylaxis.
Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 1. Flight deep vein thrombosis prophylaxis in lower limb injury	Helen Blackhurst	Focuses on flight-related deep vein thrombosis prophylaxis for lower limb injury, not specifically related to anticoagulant use for VTE in microgravity or spaceflight conditions.
Air travel and pulmonary embolism: "economy class syndrome".	Bhatia V, Arora P, Parida AK, Singh G, Kaul U.	Focuses on pulmonary embolism and deep vein thrombosis related to air travel (economy class syndrome), not specifically related to anticoagulant use or venous thromboembolism in microgravity or spaceflight conditions.
[Venous thromboembolic disease and air travel].	Sanchez O.	Focuses on venous thromboembolic disease related to air travel, not related to anticoagulant use or venous thromboembolism in microgravity or spaceflight conditions.
[What is the risk of venous thromboembolism induced by air travel and how is it managed?].	Sanchez O.	Focuses on venous thromboembolic disease related to air travel, not

		related to anticoagulant use or venous thromboembolism in microgravity or spaceflight conditions.
[The risk of venous thromboembolism during air travel].	Sanchez O.	Focuses on venous thromboembolic disease related to air travel, not related to anticoagulant use or venous thromboembolism in microgravity or spaceflight conditions.
Travel-related thrombosis: is this a problem?	Brenner B.	Focuses on venous thromboembolic disease related to air travel, not related to anticoagulant use or venous thromboembolism in microgravity or spaceflight conditions.
Routine chemoprophylaxis for travel-associated thrombosis? No.	Lubetsky A.	Does not focus on anticoagulant use or venous thromboembolism specifically in microgravity or spaceflight conditions.
[Deep-vein thrombosis and pulmonary embolism due to air travel].	Levi M, Rosendaal FR, Büller HR.	Focuses on venous thromboembolic disease related to air travel, not related to anticoagulant use or venous thromboembolism in microgravity or spaceflight conditions.
Cardiology patient pages. Prevention of deep vein thrombosis and pulmonary embolism.	Goldhaber SZ, Fanikos J.	Does not focus on anticoagulant use or venous thromboembolism in microgravity or spaceflight conditions.
The effects of flying: processes, consequences and prevention.	Shepherd L, Edwards SL.	Focuses on venous thromboembolic disease related to air travel, not related to anticoagulant use or venous thromboembolism in

		microgravity or spaceflight conditions.
[Traveler's thrombosis. Who is at risk--how to prevent it?].	Siedenburg J.	Does not focus on anticoagulant use or venous thromboembolism in microgravity or spaceflight conditions.
Medical events during airline flights.	Schuff-Werner P.	Does not focus on anticoagulant use or venous thromboembolism in microgravity or spaceflight conditions.
Prognosis of economy class syndrome treated in intensive care unit.	Hata N, Tanaka K, Imaizumi T, Ohba T, Ohara T, Shinada T, Yokoyama S, Makino T, Takano T.	Does not focus on anticoagulant use or venous thromboembolism in microgravity or spaceflight conditions.
Venous thrombosis from air travel: the LONFLIT3 study--prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial.	Cesarone MR, Belcaro G, Nicolaides AN, Incandela L, De S, Geroulakos G, Lennox A, Myers KA, Moia M, Ippolito E, Winford M.	Study focuses on air travel-related venous thrombosis, not spaceflight or microgravity conditions.
Economy class syndrome.	Sahiar F, Mohler SR.	Study does not specifically address venous thromboembolism in spaceflight or microgravity conditions. It focuses on air travel and its association with "Economy Class Syndrome," which is not related to the context of space travel.
Cerebral vascular disease, venous and arterial thrombosis	Dalen · Couch · McIntyre · Whisnant	Study focuses on cerebral vascular disease, venous, and arterial thrombosis in general, rather than specifically addressing venous thromboembolism in spaceflight or the impact of microgravity conditions.
Unilateral lower limb suspension can cause deep venous thrombosis	Bleeker, Michiel W. P.; Hopman, Maria T. E.; Rongen, Gerard A.; Smits, Paul	Study focuses on venous thrombosis caused by lower limb suspension, which is not directly related

		to spaceflight or microgravity conditions.
Effects of Exercise and Nutrition on the Coagulation System During Bedrest Immobilization	Waha, James E.; Goswami, Nandu; Schlagenhauf, Axel ; Leschnik, Bettina; Koestenberger, Martin; Reibnegger, Gilbert; Roller, Regina E.; Hinghofer-Szalkay, Helmut; Cvirn, Gerhard	Study investigates effects of exercise and nutrition on coagulation during bedrest immobilization, not in the context of microgravity or spaceflight.